Hyperkalemia After Packed Red Blood Cell Transfusion in Trauma Patients

Matthew C. Aboudara, MD, Frank P. Hurst, MD, Kevin C. Abbott, MD, and Robert M. Perkins, MD

Background: **Published analyses of clinical outcomes for patients requiring large-volume blood transfusion conflict with respect to the impact upon plasma potassium levels. We analyzed a cohort of trauma patients to ascertain the impact of component product transfusion upon plasma potassium values.**

Methods: **We performed an observational analysis of previously, prospectively collected clinical data on 131 noncrush trauma patients undergoing resuscitation during the initial 12 hours after admission to a combat support hospital. Comparisons were made between those who received packed red blood cell (PRBC) transfusion and those who did not. Primary outcome was hyperkalemia (plasma potassium level >5.5 mmol/L).**

Results: **Ninety-six of one hundred thirty-one patients (73.3%) received PRBCs (mean number of PRBC units 11.2, range, 0–55.0). For transfusion versus nontransfusion patients, baseline plasma potassium value (3.7 ± 0.57 mmol/L vs. 3.6 ± 0.36 mmol/L, $p = 0.22$) rose significantly after transfusion (5.3 ± 1.2 mmol/L, vs. 4.0 ± 0.78 mmol/L, $p < 0.001$). During the study period, 38.5% of transfusion patients developed hyperkalemia, versus 2.9% of those who did not ($p = 0.003$). In multivariate logistic regression analysis, transfusion of greater than 7 units of PRBCs was independently associated with the development of hyperkalemia (RR 4.72, 95% CI 1.01–21.97, $p = 0.048$). Transfusion of other cell-based products, baseline base deficits, and plasma bicarbonate levels were not. Spearman's rank correlation coefficient for the relationship of number of transfused PRBC units to the highest recorded potassium value was 0.554 ($p < 0.001$). The predictive accuracy of the logistic regression model for hyperkalemia was 0.824 (95% CI 0.747–0.901, $p < 0.001$).**

Conclusions: **Hyperkalemia is common after PRBC transfusion, and often severe. PRBC transfusion is independently associated with the development of hyperkalemia. The findings suggest the need for interventional studies examining the impact of alternative resuscitative approaches after severe trauma.**

Key words: **Potassium, Hypokalemia, Hyperkalemia.**

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A spectrum of derangements of potassium homeostasis have been reported on patients undergoing transfusion with cell-based transfusion products, specifically, packed red blood cells (PRBCs) and fresh whole blood. In both adults and children, hypokalemia has been reported more frequently than hyperkalemia. The largest reported series of which we are aware, retrospective in nature, reported an incidence of hypokalemia of 72% in children undergoing liver transplantation; hyperkalemia occurred in less than 5% of patients.[1] Others have likewise observed hypokalemia to be more common after transfusion.[2–4] In the few, small studies describing hyperkalemia after transfusion of blood products, elevations of serum potassium levels have been described alternatively as transient and "clinically insignificant".[5]

We have previously reported an independent association between the number of transfused blood products, both cell- and noncell-based, and the development of hyperkalemia in a noncrush trauma population undergoing acute resuscitation after major penetrating trauma.[6] In this population, hyperkalemia was common, often severe, but transient; however, there was a trend toward higher mortality in those patients who developed hyperkalemia compared with those who did not. To better delineate the role of cell-based transfusion, specifically PRBCs and fresh whole blood, in the development of hyperkalemia, we retrospectively analyzed data for a cohort of trauma patients undergoing acute resuscitative interventions after admission to a combat support hospital in central Iraq.

PATIENTS AND METHODS

The study was approved by the Investigational Review Board of Brooke Army Medical Center and the Research Review Committee of the 10th Combat Support Hospital. The methods have been described previously.[3] Briefly, all patients admitted to the intensive care unit with noncrush trauma were included in the analysis. Data were collected from the time of emergency room evaluation forward for 12 hours, to include all emergency room care, operative periods,

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From the Department of Internal Medicine (M.C.A.), Walter Reed Army Medical Center, Washington, DC; and Department of Internal Medicine (F.P.H., K.C.A., R.M.P.), Nephrology Service, Walter Reed Army Medical Center, Washington, DC.
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Address for reprints: Robert M. Perkins, MD, Nephrology Service/Ward 48, Walter Reed Army Medical Center, 6900 Georgia Ave NW, Washington, DC 20307; email: robert.perkins@na.amedd.army.mil.
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and intensive care. Censoring events included the end of the 12-hour study period or transfer out of the hospital.

Exclusion criteria included transfer from another health care facility, hyperkalemia or renal failure (plasma creatinine >1.5 mg/dL) at the time of initial evaluation in the emergency room or known history of chronic kidney disease, and intrahospital transfer to the ICU from locations other than the emergency room or operating room of otherwise-qualifying subjects.

We collected data on qualified subjects during a 12-hour period starting with the time of their arrival in the emergency room. For subjects who transferred out of the ICU or who died before completing the 12-hour follow-up period, data were collected and analyzed until the occurrence of the censoring event. Demographic and clinical variables were collected, to include (among others) type and quantity of all blood products and fluids received and medications administered. All surgical procedures were documented. Additionally, baseline emergency room values for base deficit and bicarbonate levels from venous blood samples were documented. All plasma potassium levels throughout the study period were recorded.

The primary outcome was the development of hyperkalemia (plasma potassium level greater than or equal to 5.5 mmol/L)[7] at any point during the study period. Secondary analyses included correlations between the number of transfused units of cell-based products (PRBCs, platelets, or fresh whole blood) and the highest recorded plasma potassium value. For the primary outcome, comparisons were made between those who were transfused PRBCs versus those who were not transfused.

Data Analysis

SPSS 12.0 (SPSS, Chicago, IL) was used for all data analyses. For the primary study endpoint, the highest recorded potassium value during the study period was used. Independent (2-sample) *t* test and Fisher's exact test were used as appropriate. Alpha values were set at 0.05 (two-tailed). The Mann-Whitney test was used as an alternative for the *t* test for continuous variables without Gaussian distribution. Logistic regression analysis was performed separately to assess factors independently associated with the development of hyperkalemia. Variables associated with *p* less than 0.05 in univariate analysis were included in the logistic regression model for multivariate analysis. Model fitness was assessed by (−2) times the natural log of the likelihood (−2LL); model variance was assessed by the Nagelkerke R^2 coefficient. Hosmer–Lemeshow testing was used to confirm model fitness. Variables that were significantly associated with *p* less than 0.05 in multivariate analysis were assumed to be independently associated with the development of hyperkalemia. A receiver operator characteristic curve was generated from the final multivariate logistic regression model to assess the predictive accuracy of the model for the development of hyperkalemia. Spearman's rank correlation coefficient was then derived to assess the association between the number of transfused PRBCs and highest recorded potassium value.

Table 1 Transfusion Characteristics of Noncrush Trauma Patients Undergoing Acute Resuscitation at a Combat Support Hospital

Variable	Study Cohort (n = 131)	Transfused PRBCs (n = 96)
Total number of transfused units*	17.3 ± 22.3	23.5 ± 23.1
Packed red blood cells (mean number of units)	8.2 ± 10.7	11.2 ± 11.1
Thawed plasma (mean number of units)	6.9 ± 8.0	9.3 ± 8.1
Fresh whole blood (mean number of units)	1.1 ± 3.8	1.5 ± 4.3
Platelets (mean number of six-pack units)	0.6 ± 1.5	0.8 ± 1.6
Cryoprecipitate (mean number of 10-pack units)	0.6 ± 1.7	0.8 ± 1.9

* Includes packed red blood cells, fresh whole blood, platelets, cryoprecipitate, and fresh frozen plasma.

RESULTS

Patients were predominantly men, and the majority (93.9%) suffered penetrating trauma. Table 1 summarizes the transfusion characteristics of the population as a whole, and the characteristics of those transfused versus those not transfused PRBCs. The predominant transfused product was PRBCs. Consistent with recent trends in combat casualty care, thawed plasma was used liberally as a resuscitative colloid as well. Fresh whole blood was also transfused when available in the most severely injured casualties.

Table 2 summarizes the laboratory data. Compared with those who did not receive a PRBC transfusion, those transfused had equivalent baseline potassium levels, but lower initial plasma bicarbonate levels and greater initial base deficits. These differences in bicarbonate level and base deficit diminished as patients underwent operative procedures and were admitted to the ICU. However, peak plasma potassium levels, which occurred predominantly during operative and early ICU periods, were markedly higher in the transfused group (Table 2).

For the primary outcome, 38.5% of the transfused group developed hyperkalemia, versus 2.9% of the nontransfused group (Table 2). In those transfused, 26 patients (27.1%) had peak plasma potassium levels greater than 6.0 mmol/L; 7 (7.3%) had levels greater than 7.0 mmol/L. Five patients died during the 12-hour study period. All of these patients received a transfusion of PRBCs, whereas no patient died in the nontransfused group. The mean number of transfused units of PRBCs in the group of patients who died was 28.8. The mean peak plasma potassium level in this group was 7.7 mmol/L. The mean plasma potassium level at the time of death was 7.4 mmol/L.

Table 2 Clinical Characteristics of Noncrush Trauma Patients Upon Admission to a Combat Support Hospital and During Acute Resuscitation

Variable	Study Cohort (n = 131)	Transfused PRBCs (n = 96)	Nontransfused (n = 35)	95% CI (p value for transfused vs nontransfused)
Age (yr)	26.8 ± 8.8	26.3 ± 7.3	27.9 ± 12.0	$p = 0.37$
Male gender, n (%)	123 (93.9)	91 (94.8)	32 (91.4)	$p = 0.44$
ER base deficit (mEq/L)	−4.3 ± 5.2	−5.3 ± 5.6	−1.6 ± 2.4	2.3–5.2 ($p < 0.01$)
ER plasma bicarbonate (mmol/L)	23 ± 3.9	22.5 ± 4.2	24.9 ± 2.6	0.8–3.9 ($p = 0.003$)
ER plasma Potassium (mmol/L)	3.7 ± 0.5	3.7 ± 0.57	3.6 ± 0.36	−0.29–0.04 ($p = 0.22$)
Peak plasma potassium (mmol/L)	4.9 ± 1.2	5.3 ± 1.2	4.0 ± 0.78	−1.6–0.86 ($p < 0.01$)
OR base deficit (mEq/L)	−4.0 ± 3.7	−4.3 ± 3.7	−2.1 ± 2.8	0.2–4.2 ($p = 0.032$)
OR plasma bicarbonate (mmol/L)	22 ± 3.3	21.9 ± 3.5	23.3 ± 2.1	−0.2–3.4 ($p = 0.173$)
ICU base deficit (mEq/L)	−2.6 ± 2.0	−2.5 ± 4.2	−2.8 ± 2.4	−2.4–1.8 ($p = 0.766$)
ICU plasma bicarbonate (mmol/L)	24 ± 2.8	24.1 ± 2.8	23.5 ± 2.9	−1.8–0.5 ($p = 0.231$)
Change in plasma potassium (mmol/L)	1.3 ± 1.2	1.56 ± 1.2	0.46 ± 0.74	−1.4–0.76 ($p < 0.01$)
Hyperkalemic (yes vs. no; n [%])	38 (29.0)	37 (38.5)	1 (2.9)	OR 21.3 (95% CI 2.9–162.5, $p = 0.003$)

Table 3 Multivariate Logistic Regression Analysis of Factors Associated With the Development of Hyperkalemia in Univariate Analysis

Covariate	RR for Hyperkalemia (95% CI)	p Value
Baseline base deficit (≤−6 mEq/L vs. >−6 mEq/L)	0.51 (0.13–1.96)	0.328
Baseline plasma bicarbonate (≤21 mmol/L vs. >21 mmol/L)	1.90 (0.51–7.10)	0.339
Total transfused products* (>10 units vs. ≤10 units)	1.69 (0.27–10.60)	0.573
Total transfused PRBCs (>7 units vs. ≤7 units)	4.72 (1.01–21.97)	0.048
Platelet transfusion (yes vs. no)	1.87 (0.46–7.67)	0.384
Cryoprecipitate transfusion (yes vs. no)	1.26 (0.34–4.65)	0.727
Fresh whole blood transfusion (yes vs. no)	1.29 (0.25–6.67)	0.760

* Includes packed red blood cells, fresh whole blood, platelets, cryoprecipitate, and fresh frozen plasma.

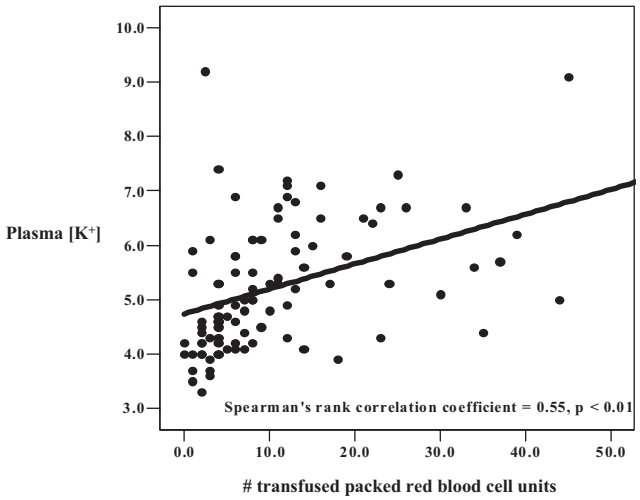

Fig. 1. *Relationship between the number of transfused PRBC units and the plasma potassium level in trauma patients undergoing acute resuscitation.*

In the logistic regression model, transfusion of more than 7 units of PRBCs (vs. less than or equal to 7 units) independently predicted hyperkalemia. Initial base deficit, plasma bicarbonate level, total transfused products, or transfusion of whole blood, cryoprecipitate, or platelets were not independently associated with the development of hyperkalemia (Table 3). Receiver operator curve analysis confirmed the predictive accuracy of our multivariate regression analysis with an area under the curve of 0.824 (95% CI 0.747–0.901, $p < 0.001$). The relationship between the number of transfused PRBC units and the plasma potassium level was modest (Spearman's rank correlation coefficient 0.55, $p < 0.01$) (Fig. 1).

DISCUSSION

In this cohort of transfused trauma patients, hyperkalemia was common, occurring in nearly 40% of those who received PRBCs. In over one quarter of this group, plasma potassium was elevated above 6.0 mmol/L, a level at which spontaneous cardiac arrhythmias may develop. Five patients died, all of whom were in the transfused group, and all of whom had severe hyperkalemia at the time of death.

Despite greater initial base deficits and lower plasma bicarbonate levels in the group ultimately transfused, baseline potassium levels were equivalent between those transfused and those who did not require transfusion. However, in the face of correcting acid base status during time, those trans-

fused developed elevated potassium levels at a higher rate than those not transfused, suggestive of a cause other than acidosis-associated hyperkalemia because of transcellular potassium and hydrogen shifts. In multivariate logistic regression, PRBC transfusion was associated with a nearly fivefold increased risk of hyperkalemia. Importantly, the transfusion of other cell-based products (including fresh whole blood) and baseline acidosis were not.

Published data on clinical outcomes associated with large-volume transfusions in trauma patients is limited, and often contradictory to the findings reported here. Sheldon et al., in a review of transfusions in critically injured patients, cite hyperkalemia as a rare occurrence, one typically associated with concomitant renal insufficiency, a group of patients excluded from this study. However, they recognize the potential role of rapid infusion as a risk factor for hyperkalemia, as have others.[8,9]

Linko and Saxelin examined, prospectively, 31 patients undergoing elective major laparotomies. Nearly 50% of those transfused more than 5 units of blood at a rate exceeding 0.3 mL/kg/min developed hyperkalemia, compared with 5% of subjects transfused lesser amounts at a rate slower than 0.3 mL/kg/min. A correlation was noted between the rate of transfusion, rather than the total amount transfused, and plasma potassium levels. In this study, as observed in our cohort, the hyperkalemia was transient, suggesting a delay in redistribution of the intravascular potassium load. Also of interest as a point of comparison with our study, fresh whole blood was used exclusively in their analysis.[10] In support of the potential importance of the rate of transfusion relative to the exogenous potassium load is Batton's case series of five newborns transfused 10 mL/kg of PRBCs at a standard rate, in which the serum potassium concentration of the component blood was as high as 23 mEq/L, yet no significant increase after transfusion in serum potassium levels was observed.[11]

Although we did not systematically track the transfusion rates for this study, a level I rapid infuser was used routinely in the initial resuscitation of the most severely injured patients, and blood products in these patients were transfused at rates faster than the at-risk group in Linko's analysis. Additionally, the mean age of the transfused PRBCs in our population was 30 days to 34 days, a point well-beyond which the extracellular potassium load within the stored unit is maximal.[12,13] Both the rate of transfusion and the age of the transfused red blood cells likely contribute to the findings reported herein.

An additional consideration in our study population is intravascular volume status; it is likely that hypovolemia secondary to ongoing hemorrhage at the time of presentation contributes to the inability to adequately redistribute a relatively large intravascular potassium load after transfusion. This triad of factors—hypovolemia and the rapid transfusion of relatively old PRBCs—may well account for the high incidence of hyperkalemia observed in this population.

To our knowledge, no interventional studies have been performed to address this complication. Several obvious interventions are impractical: promoting the renal excretion of potassium with a loop diuretic, or the use of a resin-based cathartic, are likely not safe interventions in the resuscitation of actively hemorrhaging, hypotensive patients. Rapid infusion systems are often life-saving and as such are well-established tools in the care of the most critically-injured patients, and the use of such equipment has justifiably become standard in the resuscitation of actively hemorrhaging patients.

However, several other relatively simple interventions might be considered as prophylactic strategies in higher risk patients, which we would define as those presenting with a potassium level of 4.0 mmol/L or higher and who will likely require large-volume component-blood transfusion in the acute resuscitative phase. Redistribution of a transfused load of extracellular potassium might be accelerated by a number of interventions, to include the up-front use of intravenous insulin (with infusion of glucose-containing crystalloid solutions to avoid hypoglycemia), or the use of bicarbonate infusion to ameliorate the acidosis associated with tissue hypoperfusion. Attention to the electrolyte disturbances often associated with such interventions, such as hypocalcemia with metabolic alkalosis, would be necessary. Interventions such as these might allow clinicians to "buy time" while volume status is restored with blood products. These hypotheses need to be systematically tested before their implementation as prophylactic strategies.

Our study was not designed to assess mortality. However, the observation that all deaths in the study population occurred in patients receiving large-volume PRBC transfusion and who subsequently developed severe hyperkalemia is concerning, and warrants further investigation. Given the well-known risks of even transiently elevated plasma potassium levels, particularly in a population of hemodynamically unstable patients, we think an interventional study is warranted.

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DISCUSSION

Dr. James L. Atkins (Walter Reed Army Medical Center, Washington, DC): The authors present data indicating that there is a significant incidence of at least transient hyperkalemia during or shortly after resuscitation from severe trauma and hemorrhage especially when more than 7 units of packed red blood cells are administered. The levels can be life threatening and the data is suggestive that hyperkalemia contributed to the death of several patients. The authors are to be congratulated for alerting us to this risk.

Since many blood components were administered at the same time, it is difficult to ascertain with certainty that packed RBCs is the sole culprit. The authors speculate that old packed RBCs have a high content of extracellular potassium and although potassium concentrations of the transfused products were not measured, this speculation is based on the knowledge that RBCs release intracellular potassium during storage.[1] However, these same RBCs may help to reabsorb the transfused potassium if they recover the activity of their Na or K ATPase after transfusion. Extended storage or additional damage to the RBC may decrease the likelihood that they will recover this function and this is likely the case with irradiated RBCs. The rate of rise in extracellular potassium is increased in stored RBCs after irradiation.[2] Here the incidence of hyperkalemia is so great that methods are being evaluated to reduce the transfused load of potassium including washing the RBCs,[2] altered storage solutions[1] and the inclusion of potassium absorption filters during transfusion.[3] Based on the current findings, such interventions may need to be considered for severely injured trauma patients. There is the possibility that additional RBC damage may have occurred in the present study with RBC warmers, since hyperkalemia has been associated with their use.[4] Can the authors tell us if hyperkalemia occurred more frequently when blood warmers were used?

It appears that the incidence of hyperkalemia was far greater in this population than previously seen in nontrauma patients receiving massive transfusions. In future evaluations it will be important to determine if this population was somehow unique perhaps in the use of dietary supplements before their injury, the severity of the blast associated injuries or medications prescribed in the operating room. However, there is ample evidence that trauma causes disruptions of the Na or K ATPase that could potentially translate into diminished ability to handle a potassium load during early resuscitation.

Plasma potassium increases in animal models of hemorrhagic shock and studies by Torres et al.[5] examining multiple physiologic and metabolic parameters during prolonged hypotension have found that elevated potassium was the parameter most strongly correlated with early death. It is interesting to note that two studies have shown that the survival benefit of mild hypothermia in hemorrhage correlates with slowed rate of rise in serum potassium.[6,7] The increase in potassium can be attributed in part to a defect in the function of the Na or K ATPase demonstrated in many tissues during hemorrhage[8–11] including the RBCs.[12,13] Oliver et al. have shown that this is not explained by any increase in serum quabaine like factor[14] and the detailed studies of Sayeed et al. concluded that there was an uncoupling of the Na–K-ATPase.[10] Illner and Shires made one of the first measurements of interstitial potassium in muscle during shock and levels of 10 to 15 milimolar potassium can been seen even without an increase in serum potassium.[9] These findings have recently been confirmed by modern microdialysis measurements.[14] Extracellular potassium levels in this range can cause vascular muscle relaxation and the increase in extracellular potassium may contribute to a loss of vascular responsiveness in shock. To my knowledge the timing of the recovery of Na or K ATPase activity after resuscitation has not been fully examined and if the activity of the Na/K ATPase was slow to recover after resuscitation then the casualties may be at increased risk of hyperkalemia if given large infusion of potassium early in their resuscitation.

The authors outline potential therapies for transfusion induced hyperkalemia, but it is known that the optimal treatment of hyperkalemia depends to some extent on the underlying cause and renal patients for example respond differently to some interventions for hyperkalemia. It might be prudent to consider the possibility that trauma patients may require unique therapies for hyperkalemia. In this regard the recent studies by Darlington and Gann[15] are of particular interest as these authors have shown that purine nucleosides stimulate Na or K ATPase and prolong survival in hemorrhagic shock.

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Dr. Robert M. Perkins (Walter Reed Army Medical Center, Washington, DC): Dr. Atkins raises several important issues in his response to this study. First, the underlying mechanism for the observed findings remains unclear, and we did not attempt to address this in our study design. We agree that multiple factors are likely playing a role. With respect to tissue ischemia as a source of clinically relevant hyperkalemia, we find it notable that at presentation these patients as a group were mildly hypokalemic; it was only during resuscitation that hyperkalemia was observed (although the study protocol called for exclusion of patients presenting with hyperkalemia, no patient was excluded for this indication).[1] This suggests the possibility that processes during resuscitation, as hemorrhagic shock is managed, either physiologic or iatrogenic, are contributing. The use of blood warmers and a rapid transfusion system were both employed liberally in this patient population, and we did not systematically track their use. This is certainly a limitation of our study. Others have suggested that the use of rapid transfusion systems in conjunction with the transfusion of aged red blood cells can contribute to hyperkalemia, though this remains theoretical.[2] Because of the austere conditions and technical limitations, we did not assess the extracellular potassium content of the plasma component of packed red blood cell units. However, others have reported that the potassium concentrations in the plasma component of such units stored for up to 35 days can be exceedingly high, and that the rise in potassium levels continues in a linear fashion throughout this time frame.[3,4] Finally, we have previously reported that the use of various anesthetic agents (succhinylcholine, vecuronium, etomidate, propofol, and ketamine) were not associated with the development of hyperkalemia in this cohort.[1]

Given the possibility of increased morbidity and mortality associated with the observed transient hyperkalemia in this population, and the identification of risk factors for both massive transfusion and hyperkalemia, we think that consideration of prophylactic strategies is prudent. Given the clinical acuity of, and pace of resuscitation of, most of these patients, more frequent monitoring alone may not allow for timely interventions to limit hyperkalemia. Any technology designed to clear potassium from units of stored packed red blood cells at the time of transfusion must not impede the clinical requirement for rapid transfusion. To our knowledge no such technology yet exists. It is not at all clear, as Dr. Atkins rightly points out, that standard prophylactic strategies designed to accelerate intracellular redistribution of potassium will be effective in this population, because of dysfunction of the Na–K-ATPase or other factors. We agree that further study in this area is therefore urgently warranted.

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